BA

* NOTICES *

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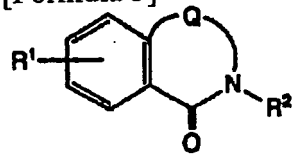
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

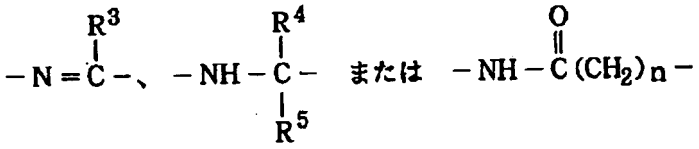
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to a bicyclic compound useful as an antirheumatic drug.
[0002]
[Description of the Prior Art] An anti-inflammatory agent, an immunotherapy agent, etc. are mentioned as a therapy agent of autoimmune diseases, such as rheumatoid arthritis, and an inflammatory disease. as an anti-inflammatory agent -- a steroid and an acid non steroid anti-inflammatory agent (indomethacin --) Non-acidity non steroid anti-inflammatory agents (mepirizole etc.), such as ketoprofen and mefenamic acid, are mentioned. As an immunotherapy agent, moreover, golden pharmaceutical preparation, D-penicillamine, levamisole, An immunity modifier and methotrexate, such as CHIOBU talitol and lobenzarit, Immunosuppresants, such as mizoribine, are large to two, and it is classified (Tomei forward happiness, Shigeto Kobayashi, and Toshikazu Hirose ., main point rheumatoid arthritis [of the pharmacotherapy in a rheumatic disease] ., the department of rheumatism, 3:339-346, 1990), and is used respectively.
[0003]
[Problem(s) to be Solved by the Invention] The conventional anti-inflammatory agent is necessarily unsatisfying in respect of effect and a side effect, although it is a symptomatic therapy agent as an agent for rheumatic diseases, it cannot become a fundamental therapy agent and an immunotherapy agent is attracting attention as cause therapy-drugs on the other hand in recent years.
[0004] Then, this invention persons provide cause therapy prevention and the therapy of an autoimmune disease with high safety, and an inflammatory disease with a strong effect with a bicyclic compound useful as drugs.
[0005]
[Means for Solving the Problem] This invention is a ** general formula (I).
[0006]
[Formula 3]

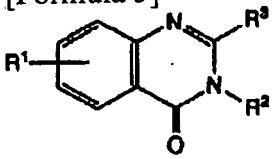


(I)

[0007] R1 means among [type the nitrogen-containing heterocycle radical which has the amino group, nitrogen-containing heterocycle radical, or substituent which has a hydrogen atom, an amino group, and a substituent. R2 means the aryl group which has an aryl group or a substituent. Q is a general formula
[0008].
[Formula 4]

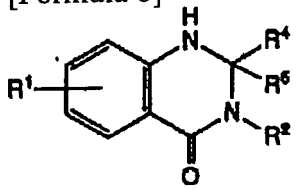


[0009] (R3 means among a formula the alkyl group which has a hydrogen atom, an alkyl group, or a substituent.) R4 means a hydrogen atom or an alkyl group. R5 means a hydrogen atom or an alkyl group. n means 1 or 2. It expresses.] The bicyclic compound come out of and shown and its salt, [0010] ** The physic, [0011] which make an active principle the bicyclic compound shown by the general formula (I), or its salt ** The preventive of the immune disease which makes an active principle the bicyclic compound shown by the general formula (I), or its salt, and/or an inflammatory disease or a therapy agent, [0012] ** The preventive or the therapy agent with unusual immunity accompanying the rheumatism or allergy which makes an active principle the bicyclic compound shown by the general formula (I), or its salt, [0013] ** The preventive of the inflammatory disease accompanying the rheumatism or allergy which makes an active principle the bicyclic compound shown by the general formula (I), or its salt or a therapy agent, [0014] ** The preventive of the bone disease which makes an active principle the bicyclic compound shown by the general formula (I), or its salt or a therapy agent, [0015] ** The antirheumatic drug which makes an active principle the bicyclic compound shown by the general formula (I), or its salt, and [0016] ** It is related with the immunosuppressive agent which makes an active principle the bicyclic compound shown by the general formula (I), or its salt.
[0017] The bicyclic compound shown by the general formula (I) of this invention can be divided roughly into the following three compounds [a general formula (Ia), a general formula (Ib), and a general formula (Ic)].
[0018]
[Formula 5]



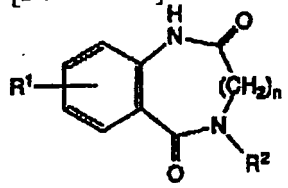
(Ia)

(R1, R2, and R3 are the same as the above among a formula.)
[0019]
[Formula 6]



(Ib)

(R1, R2, R4, and R5 are the same as the above among a formula.)
[0020]
[Formula 7]



(Ic)

(R1, R2, and n are the same as the above among a formula.)
[0021] in addition, the alkyl group used by this detail letter means the alkyl group of the shape of the shape of a straight chain, and branching, and the alkyl group which has especially 1-6 carbon atoms is

desirable, and can mention a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, the second class butyl, a tertiary butyl radical, a pentyl radical, an isopentyl radical, the second class pentyl radical, a neopentyl radical, the third class pentyl radical, a hexyl group, an iso hexyl group, etc. as an example

[0022] moreover, with the halogen atom used by this detail letter, a fluorine, a bromine, chlorine, iodine, etc. can be mentioned as an example.

[0023] Next, it explains per substituent of the bicyclic compound shown by said general formula (I).

[0024] The amino group which has a substituent in R1 may mean a monoalkylamino radical or a dialkylamino radical, and this monoalkylamino radical and the dialkylamino radical may have the substituent further on the alkyl group.

[0025] As a substituent on this alkyl group, the amino group, a monoalkylamino radical, a dialkylamino radical, etc. can be mentioned as an example.

[0026] Or two or more are contained. moreover, a "nitrogen-containing heterocycle radical" -- a nitrogen atom -- one -- Furthermore, the radical of one or five to 7 membered-ring which may be contained two or more is meant for an oxygen atom or a sulfur atom, respectively. The radical of six membered-rings which contained the radical of six membered-rings which contained two nitrogen atoms especially, the radical of six membered-rings which contained one nitrogen atom and contained one oxygen atom further, or one nitrogen atom, and contained one sulfur atom further is desirable. Specifically, a piperazinyl radical, a mol HORINIRU radical, a thia ZANIRU radical, etc. can be mentioned as an example. this nitrogen-containing heterocycle radical -- a substituent -- 1- although you may have more than one, what has especially one substituent is desirable. Especially as this substituent, an alkyl group etc. can be mentioned as an example.

[0027] In R2, a phenyl group, a biphenyl radical, a naphthyl group, an anthryl radical, a phenan tolyl group, etc. can be mentioned as an example with an "aryl group." this aryl group -- a substituent -- 1- although you may have more than one, what has especially one substituent is desirable. Although a halogen atom, a halogeno alkyl group, etc. can be mentioned as an example and this halogeno alkyl group means the alkyl group permuted by one piece or two halogen atoms or more, one sort or two sorts or more, as this substituent A mono-halogeno alkyl group, a dihalogeno alkyl group, and especially a trihalogeno alkyl group are meant. A mono-fluoro methyl group, a mono-bromomethyl radical, a monochloro methyl group, A mono-fluoro ethyl group, a mono-BUROMO ethyl group, a monochloro ethyl group, Difluoromethyl group, a dibromo methyl group, a dichloro methyl group, a difluoro ethyl group, A dibromo ethyl group, a dichloro ethyl group, a trifluoromethyl radical, a trichloromethyl radical, a trifluoroethyl radical, a TORIBUROMO ethyl group, a trichloroethyl radical, etc. can be mentioned as an example.

[0028] With the alkyl group which has a substituent in R3, what has the aforementioned nitrogen-containing heterocycle radical etc. as a substituent in an aforementioned halogeno alkyl group and this aforementioned alkyl group can be mentioned as an example.

[0029] In the bicyclic compound of this invention, the desirable substituent in substituents R1, R2, and R3 is as follows.

[0030] As R1, a hydrogen atom, the amino group, a monoalkylamino radical, a dialkylamino radical, An N-(omega-amino alkyl)-N-alkylamino radical, an N-[(omega-alkylamino) alkyl]-N-alkylamino radical, An N-[(omega-dialkylamino) alkyl]-N-alkylamino radical, The N and N-bis(omega-amino alkyl)-amino group, the N-[(omega-monoalkylamino) alkyl]-N-(omega-amino alkyl) amino group, The N-[(omega-dialkylamino) alkyl]-N-(omega-amino alkyl) amino group, The N-[(omega-dialkylamino) alkyl]-N-[(omega-monoalkylamino) alkyl] amino group, The N and N-bis[(omega-dialkylamino) alkyl] amino group, a piperazino radical, 2-alkyl piperazino radical, 3-alkyl piperazino radical, 4-alkyl piperazino radical, A 1-alkyl-2-piperazinyl radical, a 3-alkyl-2-piperazinyl radical, A 4-alkyl-2-piperazinyl radical, a 5-alkyl-2-piperazinyl radical, A 6-alkyl-2-piperazinyl radical, a 1-alkyl-3-piperazinyl radical, A 2-alkyl-3-piperazinyl radical, a 4-alkyl-3-piperazinyl radical, A 5-alkyl-3-piperazinyl radical, a 6-alkyl-3-piperazinyl radical, A morpholino group, 2-alkyl morpholino group, 3-alkyl morpholino group, 2-mol HORINIRU radical, 3-mol HORINIRU radical, a 1-alkyl-2-mol HORINIRU radical, A 3-alkyl-2-mol

HORINIRU radical, a 5-alkyl-2-mol HORINIRU radical, A 6-alkyl-2-mol HORINIRU radical, a 1-alkyl-3-mol HORINIRU radical, A 2-alkyl-3-mol HORINIRU radical, a 5-alkyl-3-mol HORINIRU radical, A 6-alkyl-3-mol HORINIRU radical, a CHIAZANO radical, 2-alkyl CHIAZANO radical, 3-alkyl CHIAZANO radical, 2-thia ZANIRU radical, 3-thia ZANIRU, a 1-alkyl-2-thia ZANIRU radical, A 3-alkyl-2-thia ZANIRU radical, a 5-alkyl-2-thia ZANIRU radical, A 6-alkyl-2-thia ZANIRU radical, a 1-alkyl-3-thia ZANIRU radical, a 2-alkyl-3-thia ZANIRU radical, a 5-alkyl-3-thia ZANIRU radical, a 6-alkyl-3-thia ZANIRU radical, etc. can be mentioned.

[0031] As R2, a phenyl group, a 2-halogeno phenyl group, a 3-halogeno phenyl group, A 4-halogeno phenyl group, 2-(halogeno alkyl) phenyl group, 3-(halogeno alkyl) phenyl group, 4-(halogeno alkyl) phenyl group, 1-naphthyl group, 2-naphthyl group, A 2-halogeno-1-naphthyl group, a 3-halogeno-1-naphthyl group, a 4-halogeno-1-naphthyl group, A 5-halogeno-1-naphthyl group, a 6-halogeno-1-naphthyl group, a 7-halogeno-1-naphthyl group, A 8-halogeno-1-naphthyl group, a 1-halogeno-2-naphthyl group, a 3-halogeno-2-naphthyl group, A 4-halogeno-2-naphthyl group, a 5-halogeno-2-naphthyl group, a 6-halogeno-2-naphthyl group, A 7-halogeno-2-naphthyl group, a 8-halogeno-2-naphthyl group, a 2-halogeno alkyl-1-naphthyl group, A 3-halogeno alkyl-1-naphthyl group, a 4-halogeno alkyl-1-naphthyl group, A 5-halogeno alkyl-1-naphthyl group, a 6-halogeno alkyl-1-naphthyl group, A 7-halogeno alkyl-1-naphthyl group, a 8-halogeno alkyl-1-naphthyl group, A 1-halogeno alkyl-2-naphthyl group, a 3-halogeno alkyl-2-naphthyl group, A 4-halogeno alkyl-2-naphthyl group, a 5-halogeno alkyl-2-naphthyl group, a 6-halogeno alkyl-2-naphthyl group, a 7-halogeno alkyl-2-naphthyl group, a 8-halogeno alkyl-2-naphthyl group, etc. can be mentioned.

[0032] As R3, a hydrogen atom, an alkyl group, a halogeno alkyl group, a piperazino alkyl group, An alkyl group, an alkyl group (3-alkyl piperazino), (2-alkyl piperazino) An alkyl group, an alkyl group (1-alkyl-2-piperazinyl), (4-alkyl piperazino) An alkyl group, an alkyl group (4-alkyl-2-piperazinyl), (3-alkyl-2-piperazinyl) An alkyl group, an alkyl group (6-alkyl-2-piperazinyl), (5-alkyl-2-piperazinyl) An alkyl group, an alkyl group (2-alkyl-4-piperazinyl), (1-alkyl-4-piperazinyl) An alkyl group, an alkyl group (5-alkyl-4-piperazinyl), (3-alkyl-4-piperazinyl) An alkyl group, a morpholino alkyl group, (6-alkyl-4-piperazinyl) An alkyl group, an alkyl group (3-alkyl morpholino), (2-alkyl morpholino) An alkyl group, an alkyl group (3-mol HORINIRU), (2-mol HORINIRU) An alkyl group, an alkyl group (3-alkyl-2-mol HORINIRU), (1-alkyl-2-mol HORINIRU) An alkyl group, an alkyl group (6-alkyl-2-mol HORINIRU), (5-alkyl-2-mol HORINIRU) An alkyl group, an alkyl group (2-alkyl-3-mol HORINIRU), (1-alkyl-3-mol HORINIRU) An alkyl group, an alkyl group (6-alkyl-3-mol HORINIRU), (5-alkyl-3-mol HORINIRU) A CHIAZANO alkyl group, an alkyl group (2-alkyl CHIAZANO), an alkyl group (3-alkyl CHIAZANO), An alkyl group, an alkyl group (3-thia ZANIRU), an alkyl group (1-alkyl-2-thia ZANIRU), (2-thia ZANIRU) An alkyl group, an alkyl group (5-alkyl-2-thia ZANIRU), (3-alkyl-2-thia ZANIRU) An alkyl group, an alkyl group (1-alkyl-3-thia ZANIRU), (6-alkyl-2-thia ZANIRU) (2-alkyl-3-thia ZANIRU) An alkyl group, an alkyl group (5-alkyl-3-thia ZANIRU), an alkyl group, etc. can be mentioned.

[0033] Among a general formula (I), in substituents R1, R2, R3, R4, and R5 and n, especially the desirable thing is as follows and its thing of such combination is desirable especially as a bicyclic compound of this invention.

[0034] As R1, as a hydrogen atom, an N-[(omega-dialkylamino) alkyl]-N-alkylamino radical and 4-alkyl piperazino radical, and R2 As a 2-halogeno phenyl group, a 4-halogeno phenyl group and 4-(halogeno alkyl) phenyl group, and R3 As a hydrogen atom, an alkyl group, a halogeno alkyl group and (4-alkyl piperazino) an alkyl group, and R4, it is 1 [0035] as an alkyl group and n as an alkyl group and R5. Among a general formula (I), in substituents R1, R2, R3, R4, and R5 and n, the most desirable thing is as follows and its thing of such combination is the most desirable as a bicyclic compound of this invention.

[0036] As R1, as a hydrogen atom, an N-[2-(dimethylamino) ethyl]-N-methylamino radical and 4-methyl piperazino radical, and R2 As 2-chlorophenyl radical, 4-chlorophenyl radical and 4-(trifluoromethyl) phenyl group, and R3 As a hydrogen atom, a methyl group, a chloromethyl radical and (4-methyl piperazino) a methyl group, and R4, it is 1 [0037] as a methyl group and n as a methyl group

and R5. Below, the example of representation of the bicyclic compound of this invention is listed. [0038] - 3-(2-halogeno phenyl)-3, 4-dihydroquinazoline-4-ON and 3-(4-halogeno phenyl)-3, 4-dihydroquinazoline-4-ON and 3-[4-(halogeno alkyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0039] - 2-alkyl-3-(2-halogeno phenyl)-3, 4-dihydroquinazoline-4-ON and 2-alkyl-3-(4-halogeno phenyl)-3, 4-dihydroquinazoline-4-ON and 2-alkyl-3-[4-(halogeno alkyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0040] - 2-halogeno alkyl-3-(2-halogeno phenyl)-3, 4-dihydroquinazoline-4-ON and 2-halogeno alkyl-3-(4-halogeno phenyl)-3, 4-dihydroquinazoline-4-ON and 2-halogeno alkyl-3-[4-(halogeno alkyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0041] - 2-(4-alkyl piperazino) alkyl-3-(2-halogeno phenyl)-3, 4-dihydroquinazoline-4-ON and 2-(4-alkyl piperazino) alkyl-3-(4-halogeno phenyl)-3, 4-dihydroquinazoline-4-ON and 2-(4-alkyl piperazino) alkyl-3-[4-(halogeno alkyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0042] - 3- (2-halogeno phenyl) -5 - 8-[N-[(omega-dialkylamino) Alkyl]-N-alkylamino] -3, 4-dihydroquinazoline-4-ON and 3-(4-halogeno phenyl)-5-8-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-3, 4-dihydroquinazoline-4-ON and 3-[4-(halogeno alkyl) phenyl]-5-8-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-3 and 4-dihydroquinazoline [0043] - 4-ON and 2-alkyl-3- (2-halogeno phenyl) -5 - 8-[N-[(omega-dialkylamino) Alkyl]-N-alkylamino] -3, 4-dihydroquinazoline-4-ON and 2-alkyl-3-(4-halogeno phenyl)-5-8-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-3, 4-dihydroquinazoline-4-ON and 2-alkyl-3-[4-(halogeno alkyl) phenyl]-5-8-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-3 and 4-dihydroquinazoline-4-ON [0044] - 2-halogeno alkyl-3- (2-halogeno phenyl) -5 - 8-[N-[(omega-dialkylamino) Alkyl]-N-alkylamino] -3, 4-dihydroquinazoline-4-ON and 2-halogeno alkyl-3-(4-halogeno phenyl)-5-8-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-3, 4-dihydroquinazoline-4-ON and 2-halogeno alkyl-3-[4-(halogeno alkyl) phenyl]-5-8-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-3 and 4-dihydroquinazoline-4-ON [0045] - 2- Alkyl-3- (4-alkyl piperazino) (2-halogeno phenyl) -5 - 8-[N-[(omega-dialkylamino) Alkyl]-N-alkylamino] -3, 4-dihydroquinazoline-4-ON and 2- Alkyl-3- (4-alkyl piperazino) (4-halogeno phenyl) -5 - 8-[N-[(omega-dialkylamino) Alkyl]-N-alkylamino] -3, 4-dihydroquinazoline-4-ON and 2-(4-alkyl piperazino) alkyl-3-[4-(halogeno alkyl) phenyl]-5-8-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-3 and 4-dihydroquinazoline-4-ON [0046] - 3- (2-halogeno phenyl) -5 - 8- (4-alkyl piperazino) -3, 4-dihydroquinazoline-4-ON and 3-(4-halogeno phenyl)-5-8-(4-alkyl piperazino)-3, 4-dihydroquinazoline-4-ON and 3-[4-(halogeno alkyl) phenyl]-5 - 8- (4-alkyl piperazino) -3, 4-dihydroquinazoline-4-ON [0047] - 2-alkyl-3- (2-halogeno phenyl) -5 - 8- (4-alkyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-alkyl-3-(4-halogeno phenyl)-5-8-(4-alkyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2-alkyl-3-[4-(Halogeno alkyl) Phenyl]-5-8-(4-alkyl piperazino)-3, 4-dihydroquinazoline-4-ON [0048] - 2-halogeno alkyl-3- (2-halogeno phenyl) -5 - 8- (4-alkyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-halogeno alkyl-3-(4-halogeno phenyl)-5-8-(4-alkyl piperazino)-3, 4-dihydroquinazoline -4 - ON and 2-halogeno alkyl-3-[4- (Halogeno alkyl) Phenyl]-5-8-(4-alkyl piperazino)-3, 4-dihydroquinazoline-4-ON [0049] - 2-Alkyl-3- (4-alkyl piperazino) (2-halogeno phenyl) -5 - 8- (4-alkyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-(4-alkyl piperazino) alkyl-3-(4-halogeno phenyl)-5-8-(4-alkyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2- (4-alkyl piperazino) Alkyl-3-[4-(halogeno alkyl) phenyl]-5-8-(4-alkyl piperazino)-3, 4-dihydroquinazoline-4-ON [0050] - 3- (2-halogeno phenyl)-2-alkyl-2-alkyl - 1, 2, 3, 4-tetrahydro quinazoline-4-ON and 3-(4-halogeno phenyl)-2-alkyl-2-alkyl - 1, 2, 3, 4 - Tetrahydro quinazoline-4-ON and 3-[4- (Halogeno alkyl) Phenyl]-2-alkyl-2-alkyl - 1, 2, 3, 4-tetrahydro quinazoline-4-ON [0051] - 3- (2-halogeno phenyl)-2-alkyl-2-alkyl-5-8-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-1 -- 4-tetrahydro quinazoline-4-ON and 2, 3, and 3- (4-halogeno phenyl)-2-alkyl-2-alkyl-5-8-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-1 -- 2, 3, 4 - Tetrahydro quinazoline-4-ON and 3-[4-(Halogeno alkyl) Phenyl]-2-alkyl-2-alkyl-5-8-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-1, 2 and 3, 4-tetrahydro quinazoline-4-ON [0052] - 3- (2-halogeno phenyl)-2-alkyl-2-alkyl-5-8-(4-alkyl piperazino)-1, 2 and 3, the 4-tetrahydro quinazoline-4-ON and 3-(4-halogeno phenyl)-2-alkyl-2-alkyl -5 - 8- (4-alkyl piperazino) 2 -1, 3, 4-tetrahydro quinazoline-4-ON and 3-[4-(halogeno alkyl) phenyl]-2-alkyl-2-alkyl-5-8-(4-alkyl piperazino)-1, 2 and 3, 4-tetrahydro quinazoline-4-ON [0053] - 4- (2-halogeno phenyl) -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(4-halogeno phenyl)-2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-[4- (Halogeno alkyl)

Phenyl] -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione [0054] - 4- (2-halogeno phenyl) -6 - 9-[N-[(omega-dialkylamino) Alkyl]-N-alkylamino] -2, 3, 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(4-halogeno phenyl)-6-9-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-2, 3 and 4, 5-tetrahydro-1H-1, The 4-benzodiazepine -2, 5-dione and 4-[4- (Halogeno alkyl) Phenyl]-6-9-[N-[(omega-dialkylamino) alkyl]-N-alkylamino]-2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione [0055] - 4- (2-halogeno phenyl) -6 - 9- (4-alkyl piperazino) -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(4-halogeno phenyl)-6-9-(4-alkyl piperazino)-2, 3 and 4, 5-tetrahydro-1H-1, 4-benzodiazepine -2, 5-dione and 4-[4-(halogeno alkyl) phenyl]-6-9-(4-alkyl piperazino)-2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione [0056] In the example of representation of the bicyclic compound of above-mentioned this invention, when two or more "alkyls" is in 1 compound, "alkyl" means an "alkyl group" which became independent and is the same and different, respectively. Moreover, "-5-8 -" and "-6-9 -" mean having an one-piece substituent in either of the 8th place and the 6th place to the 9th place from the 5th place of a basic frame, respectively.

[0057] Below, the example of the bicyclic compound of this invention is listed.
[0058] - 3-(2-chlorophenyl)-3, 4-dihydroquinazoline-4-ON and 3-(4-chlorophenyl)-3, 4-dihydroquinazoline-4-ON and 3-[4-(trifluoromethyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0059] - 2-methyl-3-(2-chlorophenyl)-3, 4-dihydroquinazoline-4-ON and 2-methyl-3-(4-chlorophenyl)-3, 4-dihydroquinazoline-4-ON and 2-methyl-3-[4-(trifluoromethyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0060] - 2-chloromethyl-3-(2-chlorophenyl)-3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-(4-chlorophenyl)-3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-[4-(trifluoromethyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0061] - 2-(4-methyl piperazino) methyl-3-(2-chlorophenyl)-3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-(4-chlorophenyl)-3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-[4-(trifluoromethyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0062] - 3- (2-chlorophenyl)-5-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] 4-dihydroquinazoline-4-ON and -3, 4-dihydroquinazoline-4-ON and 3-(2-chlorophenyl)-6-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, and 3- (2-chlorophenyl)-7-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 3-(2-chlorophenyl)-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON [0063] - 3- (4-chlorophenyl)-5-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] 4-dihydroquinazoline-4-ON and -3, 4-dihydroquinazoline-4-ON and 3-(4-chlorophenyl)-6-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, and 3- (4-chlorophenyl)-7-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 3-(4-chlorophenyl)-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON [0064] - 3-[4- Phenyl]-5-[N-[2- (Trifluoromethyl) (Dimethylamino) Ethyl]-N-methylamino] -3, 4 - Dihydroquinazoline-4-ON and 3-[4- Phenyl]-6-[N-[2- (Trifluoromethyl) (Dimethylamino) Ethyl]-N-methylamino] -3, 4 - Dihydroquinazoline-4-ON and 3-[4- Phenyl]-7-[N-[2- (Trifluoromethyl) (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 3-[4-(trifluoromethyl) phenyl]-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3 and 4-dihydroquinazoline-4-ON [0065] - 2-methyl-3- (2-chlorophenyl)-5-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-methyl-3- (2-chlorophenyl)-6-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-methyl-3- (2-chlorophenyl)-7-[N-[2-(Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-methyl-3-(2-chlorophenyl)-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON [0066] - 2-methyl-3- (4-chlorophenyl)-5-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-methyl-3- (4-chlorophenyl)-6-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-methyl-3- (4-chlorophenyl)-7-[N-[2-(Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-methyl-3-(4-chlorophenyl)-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON [0067] - 2-methyl-3-[4- Phenyl]-5-[N-[2- (Trifluoromethyl) (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-methyl-3-[4-(trifluoromethyl) phenyl]-6-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON and 2-methyl-3-[4- Phenyl]-7-[N-[2- (Trifluoromethyl)

(Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-methyl-3-[4-(trifluoromethyl) phenyl]-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON [0068] - 2-chloromethyl-3-(2-chlorophenyl)-5-[N-[2-(dimethylamino) ethyl]-N-methylamino] - 3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-(2-chlorophenyl)-6-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3- (2-chlorophenyl)-7-[N-[2-(Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-(2-chlorophenyl)-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON [0069] - 2-chloromethyl-3- (4-chlorophenyl)-5-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3- (4-chlorophenyl)-6-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3- (4-chlorophenyl)-7-[N-[2-(Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-(4-chlorophenyl)-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON [0070] - 2-chloromethyl-3-[4- Phenyl]-5-[N-[2- (Trifluoromethyl) (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-[4-(trifluoromethyl) phenyl]-6-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 2-chloromethyl-3-[[quinazoline-4-ON and]4- 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-[4-(trifluoromethyl) phenyl]-7-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3 and 4-dihydro -- (Trifluoromethyl) Phenyl]-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON [0071] - 2- Methyl-3- (4-methyl piperazino) (2-chlorophenyl)-5-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-(2-chlorophenyl)-6-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON and 2- Methyl-3- (4-methyl piperazino) (2-chlorophenyl)-7-[N-[2-(Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-(2-chlorophenyl)-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON [0072] - 2- Methyl-3- (4-methyl piperazino) (4-chlorophenyl)-5-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-(4-chlorophenyl)-6-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON and 2- Methyl-3- (4-methyl piperazino) (4-chlorophenyl)-7-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-(4-chlorophenyl)-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON [0073] - 2- Methyl-3-[4- (4-methyl piperazino) Phenyl]-5-[N-[2- (Trifluoromethyl) (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-[4-(trifluoromethyl) phenyl]-6-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON and 2- Methyl-3-[4- (4-methyl piperazino) Phenyl]-7-[N-[2- (Trifluoromethyl) (Dimethylamino) Ethyl]-N-methylamino] -3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-[4-(trifluoromethyl) phenyl]-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-3, 4-dihydroquinazoline-4-ON [0074] - 3- (2-chlorophenyl)-5-(4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 3-(2-chlorophenyl)-6-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 3-(2-chlorophenyl)-7-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 3-(2-chlorophenyl)-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0075] - 3-(4-chlorophenyl)-5-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-O N and 3-(4-chlorophenyl)-6-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 3-(4-chlorophenyl)-7-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 3-(4-chlorophenyl)-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0076] - 3-[4- Phenyl]-5- (Trifluoromethyl) (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 3-[4-(trifluoromethyl) phenyl]-6-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 3-[4-(trifluoromethyl) phenyl]-7- (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 3-[4-(trifluoromethyl) phenyl]-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0077] - 2-methyl-3-(2-chlorophenyl)-5- (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-methyl-3-(2-chlorophenyl)-6-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2-methyl-3-(2-chlorophenyl)-7- (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-methyl-3-(2-chlorophenyl)-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0078] - 2-methyl-3- (4-chlorophenyl)-5- (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-methyl-3-(4-chlorophenyl)-6-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2-methyl-3-(4-chlorophenyl)-7- (4-methyl piperazino) -3, 4-

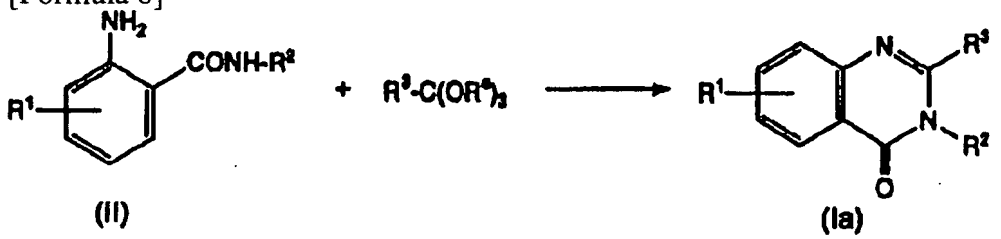
dihydroquinazoline-4-ON and 2-methyl-3-(4-chlorophenyl)-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0079] - 2-methyl-3-[4- Phenyl]-5- (Trifluoromethyl) (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-methyl-3-[4-(trifluoromethyl) phenyl]-6-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2-methyl-3-[4- (Trifluoromethyl) Phenyl]-7-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2-methyl-3-[4-(trifluoromethyl) phenyl]-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0080] - 2-chloromethyl-3- (2-chlorophenyl)-5- (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-(2-chlorophenyl)-6-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-(2-chlorophenyl)-7- (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-(2-chlorophenyl)-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0081] - 2-chloromethyl-3- (4-chlorophenyl)-5- (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-(4-chlorophenyl)-6-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-(4-chlorophenyl)-7- (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-chloromethyl-3-(4-chlorophenyl)-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0082] - 2-chloro alkyl-3-[4- Phenyl]-5- (Trifluoromethyl) (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-chloro alkyl-3-[4-(trifluoromethyl) phenyl]-6-(4-methyl piperazino)-3, 4-dihydroquinazoline -4 - ON and 2-chloro alkyl-3-[4- Phenyl]-7-(Trifluoromethyl) (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-chloro alkyl-3-[4-(trifluoromethyl) phenyl]-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0083] - 2- Methyl-3-(4-methyl piperazino) (2-chlorophenyl)-5- (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-(2-chlorophenyl)-6-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3- (2-chlorophenyl)-7-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-(2-chlorophenyl)-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0084] - 2-(4-methyl piperazino) methyl-3-(4-chlorophenyl)-5-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl -3 - (4) - Chlorophenyl-6- (4-methyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-(4-chlorophenyl)-7-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3- (4-chlorophenyl)-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0085] - 2- Methyl-3-[4- (4-methyl piperazino) Phenyl]-5- (Trifluoromethyl) (4-alkyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-[4-(trifluoromethyl) phenyl]-6-(4-alkyl piperazino)-3, 4-dihydroquinazoline-4-ON and 2- Methyl-3-[4- (4-methyl piperazino) Phenyl]-7-(Trifluoromethyl) (4-alkyl piperazino) -3, 4-dihydroquinazoline-4-ON and 2-(4-methyl piperazino) methyl-3-[4-(trifluoromethyl) phenyl]-8-(4-alkyl piperazino)-3, 4-dihydroquinazoline-4-ON [0086] - 3-(2-chlorophenyl)-2 and 2-dimethyl - 1, 2, 3, 4-tetrahydro quinazoline-4-ON and 3-(4-chlorophenyl)-2, and 2-dimethyl - 1, 2, 3, 4-tetrahydro quinazoline-4-ON and 3-[4-(trifluoromethyl) phenyl]-2, and 2-dimethyl - 1, 2, 3, 4-tetrahydro quinazoline-4-ON [0087] - 3- (2-chlorophenyl) -2 and 2-dimethyl-5-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] 2 -1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-(2-chlorophenyl)-2, 2-dimethyl-6-[N-[2-(dimethylamino) ethyl]-N-methylamino]-1, 3, 4-tetrahydro quinazoline-4-ON and 3- (2-chlorophenyl) -2 and 2-dimethyl-7-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] 2 -1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-(2-chlorophenyl)-2, 2-dimethyl-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-1, 3, 4-tetrahydro quinazoline-4-ON [0088] - 3- (4-chlorophenyl) -2 and 2-dimethyl-5-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] 2 -1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-(4-chlorophenyl)-2, 2-dimethyl-6-[N-[2-(dimethylamino) ethyl]-N-methylamino]-1, 3, 4-tetrahydro quinazoline-4-ON and 3- (4-chlorophenyl) -2 and 2-dimethyl-7-[N-[2-(Dimethylamino) Ethyl]-N-methylamino] 2 -1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-(4-chlorophenyl)-2, 2-dimethyl-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-1, 3, 4-tetrahydro quinazoline-4-ON [0089] - 3-[4- (Trifluoromethyl) Phenyl] -2, 2-dimethyl-5-[N-[2-(dimethylamino) ethyl]-N-methylamino]-1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-[4-(trifluoromethyl) phenyl]-2, 2-dimethyl-6-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] 2 -1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-[4-(trifluoromethyl) phenyl]-2, 2-dimethyl-7-[N-[2-(dimethylamino) ethyl]-N-methylamino]-1, 3, 4-tetrahydro quinazoline-4-ON and 3-[4-(trifluoromethyl) phenyl]-2, 2-dimethyl-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-1, 2 and 3, 4-tetrahydro quinazoline-4-ON [0090] - 3- (2-

chlorophenyl) -2 and 2-dimethyl-5- (4-methyl piperazino) -1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-(2-chlorophenyl)-2, 2-dimethyl-6-(4-methyl piperazino)-1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3- (2-chlorophenyl) -2 and 2-dimethyl-7- (4-methyl piperazino) -1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-(2-chlorophenyl)-2, 2-dimethyl-8-(4-methyl piperazino)-1, 2 and 3, 4-tetrahydro quinazoline-4-ON [0091] - 3- (4-chlorophenyl) -2 and 2-dimethyl-5- (4-methyl piperazino) -1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-(4-chlorophenyl)-2, 2-dimethyl-6-(4-methyl piperazino)-1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3- (4-chlorophenyl) -2 and 2-dimethyl-7- (4-methyl piperazino) -1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-(4-chlorophenyl)-2, 2-dimethyl-8-(4-methyl piperazino)-1, 2 and 3, 4-tetrahydro quinazoline-4-ON [0092] - 3-[4- (Trifluoromethyl) Phenyl] -2 and 2-dimethyl-5- (4-methyl piperazino) -1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-[4-(trifluoromethyl) phenyl]-2, 2-dimethyl-6-(4-methyl piperazino)-1, 2, 3, 4 - Tetrahydro quinazoline-4-ON and 3-[4- (Trifluoromethyl) Phenyl] -2 and 2-dimethyl-7- (4-methyl piperazino) -1, 2 and 3, 4-tetrahydro quinazoline-4-ON and 3-[4-(trifluoromethyl) phenyl]-2, 2-dimethyl-8-(4-methyl piperazino)-1, 2 and 3, 4-tetrahydro quinazoline-4-ON [0093] - 4-(2-chlorophenyl)-2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(4-chlorophenyl)-2, 3 and 4, 5-Thet RAHIDORO-1H-1, the 4-benzodiazepine -2, 5-dione and 4-[4-(trifluoromethyl) phenyl]-2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione [0094] - 4- (2-chlorophenyl)-6-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] 3 -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(2-chlorophenyl)-7-[N-[2-(dimethylamino) ethyl]-N-methylamino]-2, 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(2-chlorophenyl)-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4- (2-chlorophenyl)-9- [N-[2-(dimethylamino) ethyl]-N-methylamino] -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, and 5-dione [0095] - 4- (4-chlorophenyl)-6-[N-[2- (Dimethylamino) Ethyl]-N-methylamino] 3 -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(4-chlorophenyl)-7-[N-[2-(dimethylamino) ethyl]-N-methylamino]-2, 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(4-chlorophenyl)-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4- (4-chlorophenyl)-9- [N-[2-(dimethylamino) ethyl]-N-methylamino] -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, and 5-dione [0096] - 4-[4- Phenyl]-6-[N-[2-(Trifluoromethyl) (Dimethylamino) ethyl]-N-methylamino] -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, and 5-dione and 4-[4-(trifluoromethyl) phenyl]-7-[N-[2-(dimethylamino) ethyl]-N-methylamino] - 2 and 3 -- 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-[4-(trifluoromethyl) phenyl]-8-[N-[2-(dimethylamino) ethyl]-N-methylamino]-2, 3 and 4, 5-tetrahydro-1H-1, The 4-benzodiazepine -2, 5-dione and 4-[4-(trifluoromethyl) phenyl]-9-[N-[2-(dimethylamino) ethyl]-N-methylamino]-2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione [0097] - 4- (2-chlorophenyl)-6- (4-methyl piperazino) -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(2-chlorophenyl)-7-(4-methyl piperazino)-2, 3 and 4, 5-tetrahydro-1H-1, 4-benzodiazepine -2, 5-dione and 4- (2-chlorophenyl)-8- (4-methyl piperazino) -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(2-chlorophenyl)-9-(4-methyl piperazino)-2, 3 and 4, 5-tetrahydro-1H-1, 4-benzodiazepine -2, 5-dione [0098] - 4- (4-chlorophenyl)-6- (4-methyl piperazino) -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(4-chlorophenyl)-7-(4-methyl piperazino)-2, 3 and 4, 5-tetrahydro-1H-1, 4-benzodiazepine -2, 5-dione and 4- (4-chlorophenyl)-8- (4-methyl piperazino) -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-(4-chlorophenyl)-9-(4-methyl piperazino)-2, 3 and 4, 5-tetrahydro-1H-1, 4-benzodiazepine -2, 5-dione [0099] - 4-[4-Phenyl]-6- (Trifluoromethyl) (4-methyl piperazino) -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-[4-(trifluoromethyl) phenyl]-7-(4-methyl piperazino)-2, 3 and 4, 5-tetrahydro-1H-1, The 4-benzodiazepine -2, 5-dione and 4-[4- Phenyl]-8- (Trifluoromethyl) (4-methyl piperazino) -2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione and 4-[4-(trifluoromethyl) phenyl]-9-(4-methyl piperazino)-2, 3 and 4, 5-tetrahydro-1H-1, The 4-benzodiazepine -2, 5-dione [0100] Next, the manufacture approach of the bicyclic compound of this invention is explained.

[0101] The manufacture approach 1 [composition of a general formula (Ia)]

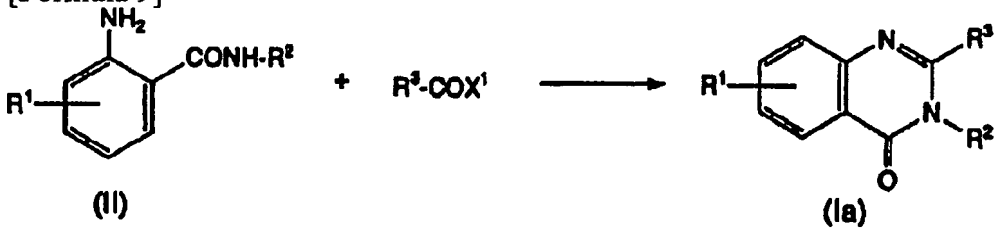
[0102]

[Formula 8]



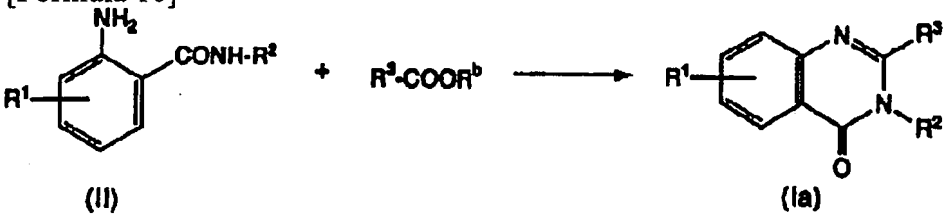
(II) (Ia)

(R1, R2, and R3 are the same as the above among a formula.) Ra means an alkyl group.
[0103] The manufacture approach 2 [composition of a general formula (Ia)]
[0104]
[Formula 9]



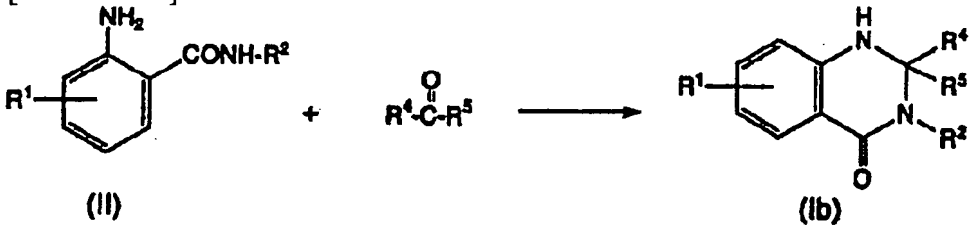
(II) (Ia)

(R1, R2, and R3 are the same as the above among a formula.) X1 means a halogen atom.
[0105] The manufacture approach 3 [composition of a general formula (Ia)]
[0106]
[Formula 10]



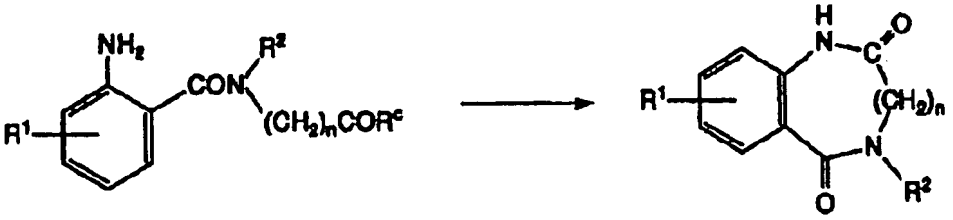
(II) (Ia)

(R1, R2, and R3 are the same as the above among a formula.) Rb means an alkyl group.
[0107] The manufacture approach 4 [composition of a general formula (Ib)]
[0108]
[Formula 11]



(II) (Ib)

(R1, R2, R4, and R5 are the same as the above among a formula.)
[0109] The manufacture approach 5 [composition of a general formula (Ic)]
[0110]
[Formula 12]



(III) (Ic)

(R1, R2, and n are the same as the above among a formula.) Rc means an alkyl group.

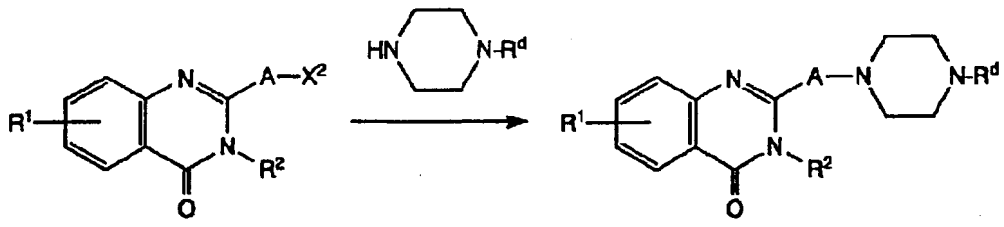
[0111] The manufacture approach 1 is enforced under existence of a solvent inactive for this reaction, or un-existing. As a solvent which can be used for this reaction, benzene, toluene, a xylene, a chlorobenzene, a nitrobenzene, chloroform, 1,2-dichloroethane, a carbon tetrachloride, etc. can be mentioned as an example. The above-mentioned solvent may mix and use two or more sorts. Moreover, this reaction can be carried out under existence of an acid catalyst or un-existing. As an acid catalyst which can be used, organic acids, such as p-toluenesulfonic acid besides mineral acids, such as a sulfuric acid, a hydrochloric acid, and a boron trifluoride, methansulfonic acid, trifluoroacetic acid, and trifluoro methansulfonic acid, can also be mentioned as an example. Moreover, although reaction temperature and especially reaction time are not limited, the range of reaction temperature of 20 degrees C - 250 degrees C is desirable, and especially its range that is 60 degrees C - 150 degrees C is desirable. The range of reaction time of 0.1 - 10 hours is desirable, and it is desirable. [of especially the range of 0.5 - 2 hours]

[0112] The manufacture approach 2 is enforced under existence of a solvent inactive for this reaction, or un-existing. As a solvent which can be used for this reaction, benzene, toluene, a xylene, a chlorobenzene, a nitrobenzene, chloroform, 1,2-dichloroethane, a carbon tetrachloride, etc. can be mentioned as an example. The above-mentioned solvent may mix and use two or more sorts. Moreover, this reaction can be carried out under existence of a base or un-existing. As a base which can be used, organic bases, such as triethylamine besides inorganic bases, such as potassium carbonate, a sodium carbonate, a sodium hydrogencarbonate, a potassium hydrogencarbonate, a calcium carbonate, a calcium hydroxide, a calcium oxide, and magnesium oxide, tripropylamine, a pyridine, and picoline, can also be mentioned as an example. Moreover, although reaction temperature and especially reaction time are not limited, the range of reaction temperature of 50 degrees C - 250 degrees C is desirable, and especially its range that is 60 degrees C - 150 degrees C is desirable. The range of reaction time of 0.1 - 20 hours is desirable, and it is desirable. [of especially the range of 2 - 10 hours] In addition, when R3 is the alkyl group which has a substituent, in case the substituent in this alkyl group is a halogen atom, the nitrogen-containing heterocycle further described above may be made to react.

[0113] Next, the following reactions are mentioned as an example.

[0114]

[Formula 13]



(R1 and R2 are the same as the above among a formula.) A means an alkylene group. X2 means a halogen atom. Rd means an alkyl group.

[0115] The manufacture approach 3 is enforced under existence of a solvent inactive for this reaction, or un-existing. As a solvent which can be used for this reaction, high-boiling point solvents, such as N.N-dimethylformamide, N, and N-dimethyl acetamido, N-methyl pyrrolidone, a biphenyl, diphenyl ether,

and the Dow-Jones therm A (Dow Chemical Co. make), can be mentioned as an example. The above-mentioned solvent may mix and use two or more sorts. Moreover, although reaction temperature and especially reaction time are not limited, the range of reaction temperature of 100 degrees C - 250 degrees C is desirable, and especially its range that is 150 degrees C - 200 degrees C is desirable. The range of reaction time of 1 - 100 hours is desirable, and it is desirable. [of especially the range of 2 - 24 hours]

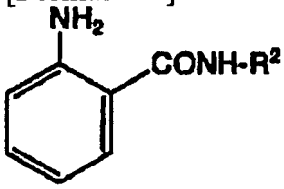
[0116] The manufacture approach 4 is enforced under existence of a solvent inactive for this reaction, or un-existing. As a solvent which can be used for this reaction, benzene, toluene, a xylene, a chlorobenzene, a nitrobenzene, chloroform, 1,2-dichloroethane, a carbon tetrachloride, etc. can be mentioned as an example. The above-mentioned solvent may mix and use two or more sorts. Moreover, this reaction can be carried out under existence of a catalyst or un-existing. As an acid catalyst which can be used, organic acids, such as p-toluenesulfonic acid besides mineral acids, such as a sulfuric acid, a hydrochloric acid, and a boron trifluoride, methansulfonic acid, trifluoroacetic acid, and trifluoro methansulfonic acid, can also be mentioned as an example. Moreover, although reaction temperature and especially reaction time are not limited, the range of reaction temperature of 10 degrees C - 100 degrees C is desirable, and especially its range that is 20 degrees C - 60 degrees C is desirable. Reaction time The range of 0.1 - 10 hours is desirable, and especially the range of 0.2 - 1 hour is desirable.

[0117] The manufacture approach 5 is enforced under existence of a solvent inactive for this reaction, or un-existing. As a solvent which can be used for this reaction, benzene, toluene, xylene, chlorobenzene, nitrobenzene, chloroform, 1,2-dichloroethane, N.N-dimethylformamide, N, and N-dimethyl acetamido, N-methyl pyrrolidone, etc. can be mentioned as an example. The above-mentioned solvent may mix and use two or more sorts. Moreover, this reaction can be carried out under existence of a catalyst or un-existing. As a catalyst which can be used, triethylamine, sodium hydride, a sodium hydroxide, etc. can be mentioned as an example. Moreover, although reaction temperature and especially reaction time are not limited, the range of reaction temperature of 100 degrees C - 250 degrees C is desirable, and especially its range that is 150 degrees C - 200 degrees C is desirable. The range of reaction time of 1 - 240 hours is desirable, and it is desirable. [of especially the range of 2 - 96 hours]

[0118] The general formula (II) which is a raw material at the time of manufacturing the bicyclic compound of this invention is divided roughly into two compounds, a general formula (IIa) and a general formula (IIb).

[0119]

[Formula 14]

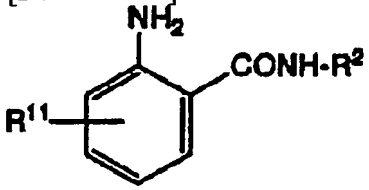


(IIa)

(R2 is the same as the above among a formula.)

[0120]

[Formula 15]



(IIb)

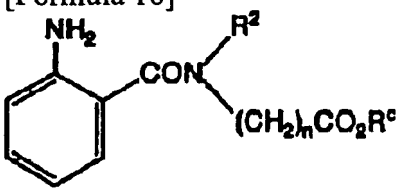
(R11 means among a formula the nitrogen-containing heterocycle radical which may have the amino group, nitrogen-containing heterocycle radical, or substituent which has an amino group and a substituent.) R2 is the same as the above.

[0121] The general formula (III) which is a raw material at the time of manufacturing the bicyclic

compound of this invention is divided roughly into two compounds, a general formula (IIIa) and a general formula (IIIb).

[0122]

[Formula 16]

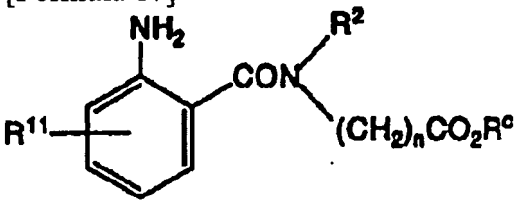


(IIIa)

(R2, n, and Rc are the same as the above among a formula.)

[0123]

[Formula 17]



(IIIb)

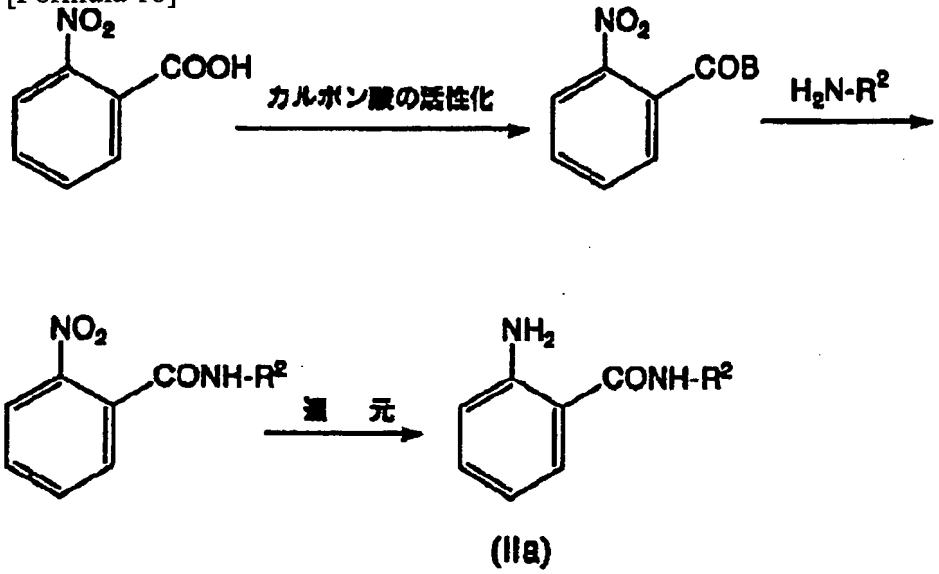
(R11, R2, n, and Rc are the same as the above among a formula.)

[0124] The compound shown by the general formula (IIa) which is a raw material at the time of manufacturing the bicyclic compound of this invention, the general formula (IIb), the general formula (IIIa), and the general formula (IIIb) can be manufactured by the following approaches.

[0125] The manufacture approach 6 [composition of a general formula (IIa)]

[0126]

[Formula 18]



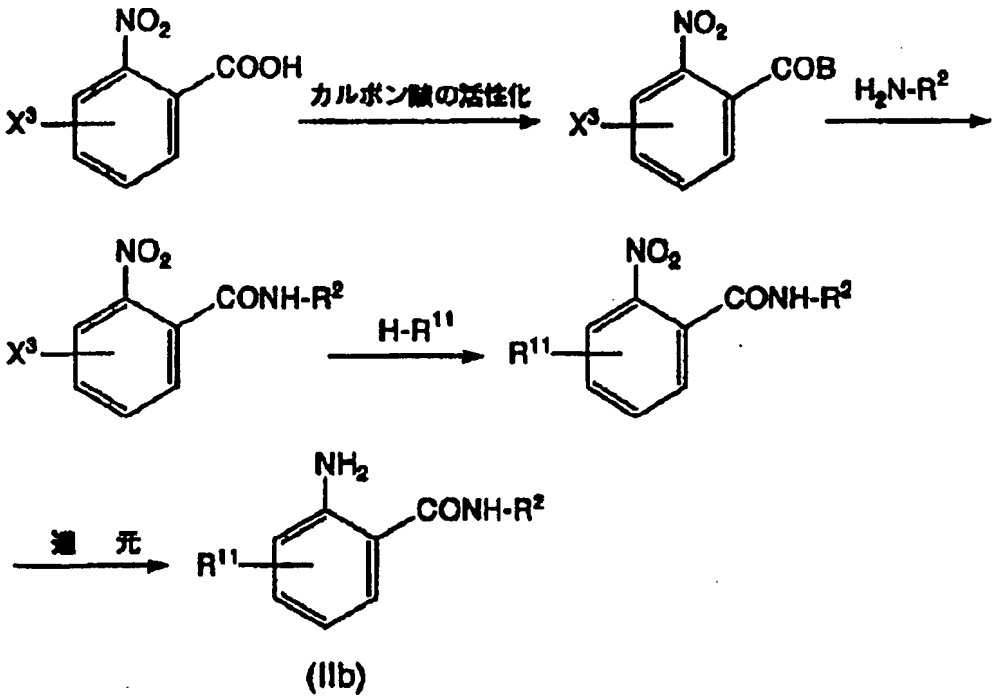
(IIa)

(R2 is the same as the above among a formula.) B means the leaving group of the activated carboxylic-acid derivative.

[0127] The manufacture approach 7 [composition of a general formula (IIb)]

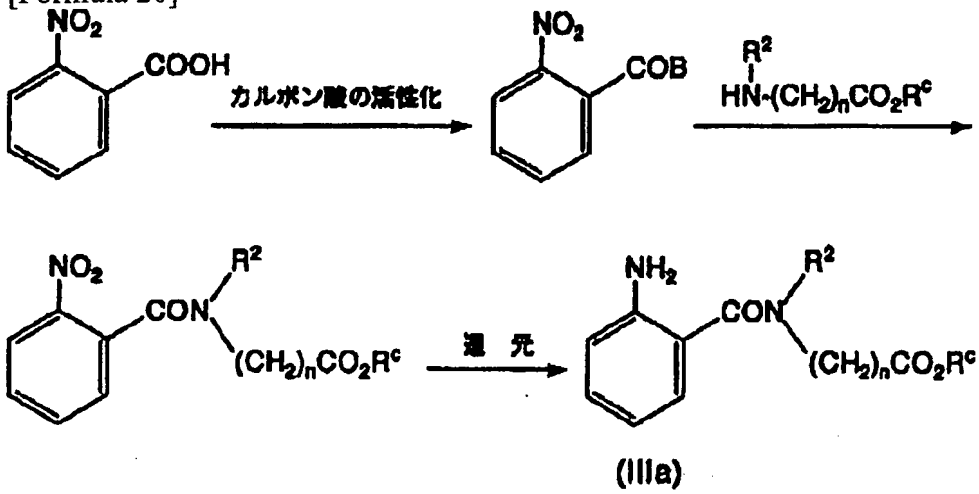
[0128]

[Formula 19]



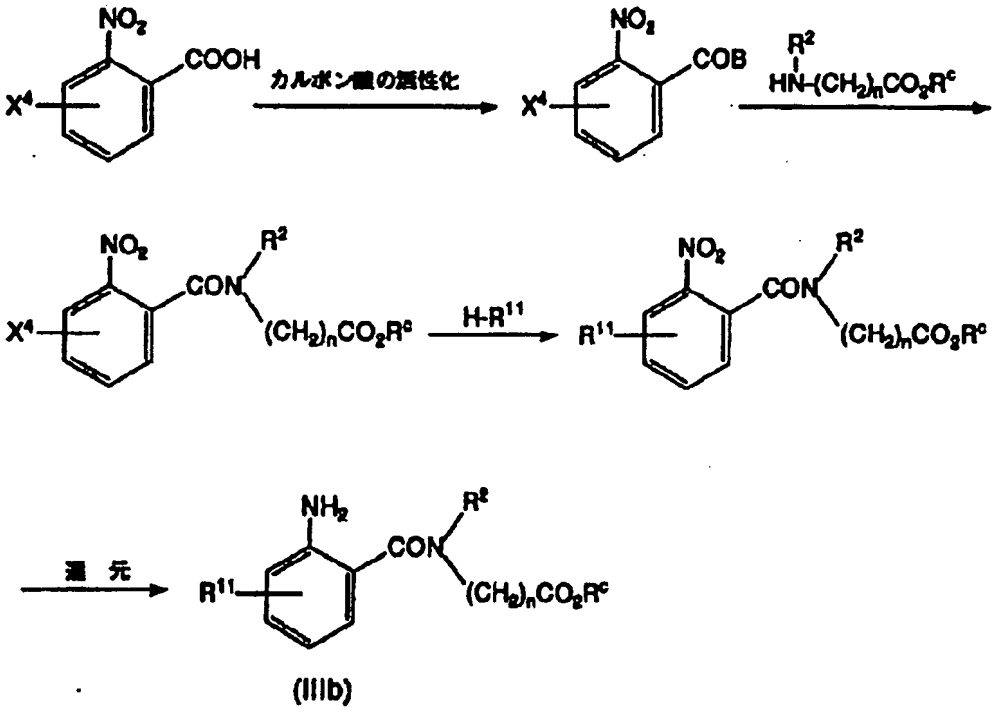
(IIb)

(R11, R2, and B are the same as the above among a formula.) X3 means a halogen atom.
[0129] The manufacture approach 8 Composition [of a general formula (IIIa)]]
[0130]
[Formula 20]



(IIIa)

(R2, Rc, n, and B are the same as the above among a formula.)
[0131] The manufacture approach 9 [composition of a general formula (IIIb)]
[0132]
[Formula 21]



(IIIb)

(R11, R2, Rc, n, and B are the same as the above among a formula.) X4 means a halogen atom.
[0133] the dicyclohexylcarbodiimide (DCC) used for activation of the above-mentioned carboxylic acid at general peptide synthesis besides an acid chloride method -- it can carry out by law, the azide method, the activity ester method, the symmetry acid-anhydride method, and the mixed acid anhydride method.
[0134] The radical expressed with C6H 11 N=C(C6H11NH) O- drawn from a halogen atom, the third class butyloxy carbonyloxy group, an isoamyl oxycarbonyl oxy-radical, p-nitrophenyloxy radical, a succinimid oxy-radical, a benzotriazoryl oxy-radical, an azide radical, an imidazolyl radical, and DCC, such as chlorine, as a concrete radical of B, for example can be mentioned as an example.
[0135] The manufacture approaches 6, 7, 8, and 9 are enforced under existence of a solvent inactive for this reaction, or un-existing. As a solvent which can be used for this reaction, benzene, toluene, a xylene, a methylene chloride, chloroform, 1,2-dichloroethane, a tetrahydrofuran, ethyl ether, etc. can be mentioned as an example. The above-mentioned solvent may mix and use two or more sorts. Moreover, this reaction can be carried out under existence of a catalyst or un-existing. Although organic bases, such as triethylamine besides inorganic bases, such as potassium carbonate, a sodium carbonate, a sodium hydrogencarbonate, a potassium hydrogencarbonate, a calcium carbonate, a calcium hydroxide, a calcium oxide, and magnesium oxide, tripropylamine, N-methyl morpholine, a pyridine, and picoline, can also be mentioned as an example and reaction temperature and especially reaction time are not limited as a catalyst which can be used, the range of reaction temperature of -20 degrees C - 100 degrees C is desirable, and especially its range that is 5 degrees C - 30 degrees C is desirable. The range of reaction time of 0.1 - 10 hours is desirable, and it is desirable. [of especially the range of 0.5 - 2 hours]
[0136] The physic which makes an active principle the bicyclic compound of this invention or its salt can be used as prevention or the therapy agent of prevention or the therapy agent of the inflammatory disease accompanying the prevention or the therapy agent with unusual immunity accompanying prevention or the therapy agent of ** immunity disease and/or an inflammatory disease, ** rheumatism, or allergy, ** rheumatism, or allergy, and ** bone disease, ** antirheumatic drug, and a ** immunosuppressive agent.
[0137] Taking orally or a parenteral target can be medicated with the physic which makes an active principle the bicyclic compound of this invention, or its salt.
[0138] Physic which makes an active principle the bicyclic compound of this invention or its salt can be pharmaceutical-preparation-ized to various pharmaceutical forms with a well-known pharmaceutical

preparation technique, and suitable additives, such as the excipient and binder which are usually used, and disintegrator, can be added into pharmaceutical preparation.
[0139] The additive which can be added into pharmaceutical preparation must be harmless in the dose of pharmaceutical preparation, and does not carry out the failure of the effectiveness by the active principle of pharmaceutical preparation.
[0140] As an excipient which can be used, a lactose, starch, crystalline cellulose, light anhydrous silicic acid, etc. can be mentioned.
[0141] As a binder which can be used, a mannitol, a dextrin, hydroxypropylcellulose, a polyvinyl pyrrolidone, etc. can be mentioned.
[0142] As disintegrator which can be used, starch, a carboxymethyl cellulose, carboxymethyl-cellulose calcium, etc. can be mentioned.
[0143] As an oral agent, the medicinal example of pharmaceutical preparation which makes an active principle the bicyclic compound of this invention or its salt can mention a capsule, a granule, a fine grain agent, a pill, powder, a tablet, etc., and can mention injections, a percutaneous absorption agent, etc. as a parenteral agent.
[0144] During time before a meal and a meal, after a meal, etc. are possible for an administration stage in case the physic which makes an active principle the bicyclic compound of this invention or its salt is offered as an oral agent, and it may be ****(ed) to about 1 - 3 times on the 1st.
[0145] The active principle is [1-2500mg] suitable per adult for one day, and 50-500mg of medicinal doses which make an active principle the bicyclic compound of this invention or its salt is usually 100-200mg especially preferably preferably.
[0146] Although the example of reference, an example, and the example of a trial are given to below and this invention is further explained to it at a detail, this invention should not be limited to these.
[0147]
[Related Example(s)]
Example of reference 1.3-chloro-N-(4-chlorophenyl)-2-nitro benzamide [0148] 3-chloro-2-nitro benzoic acid 40.0g, thionyl chloride The heating reflux of the mixture of the dimethylformamide of 20ml and the amount of catalysts was carried out for 90 minutes. It is a methylene chloride about the acid chloride which distilled off the superfluous thionyl chloride after cooling and was obtained. It was made to dissolve in 100ml and used for the next reaction.
[0149] p-chloroaniline 25.3g and pyridine It is a methylene chloride about 19.3ml. It was made to dissolve in 200ml and the methylene chloride solution of the acid chloride previously obtained under ice-cooling was dropped. The solvent was distilled off for reaction mixture after 3-hour churning at the room temperature. The obtained residue is poured out into iced water, the depositing crystal is separated, and it recrystallizes [ethanol] after rinsing, and is a 3-chloro-N-(4-chlorophenyl)-2-nitro benzamide. 56.8g (95% of yield) was obtained as a colorless crystal. The 170 to 172 degree C melting point.
[0150] Elemental-analysis value It is [0151] as C13H8Cl2N 2O3.
C(%) H(%) N(%)
Calculated value: 50.18 : 2.59 : 9.01
Actual measurement: 50.23 : 2.26 : 8.84
[0152] 1 H-NMR (DMSO-d6) delta: -- 7.34 (2H, d), 7.70 (2H, d), and 7.80- 7.90 (3H, m) and 10.85 (1H, br s)
[0153] Example of reference 2.N-(4-chlorophenyl)-3-(4-methyl piperazino)-2-nitro benzamide [0154] 3-chloro-N-(4-chlorophenyl)-2-nitro benzamide obtained in the example 1 of reference under nitrogen-gas-atmosphere mind 15.0g and 1-methyl piperazine 16.9g mixture was agitated at 100 to 105 degree C for 2 hours. Ethanol after cooling a reaction mixture It dilutes with 30ml, the crystal which poured and deposited in iced water is ******ed from the ethanol after separation, rinsing, and desiccation, and it is an N-(4-chlorophenyl)-3-(4-methyl piperazino)-2-nitro benzamide. 178.0g (98.5%) was obtained as light yellow prism **. The 188 to 190 degree C melting point.
[0155] Elemental-analysis value It is [0156] as C18H19ClN 4O3.
C(%) H(%) N(%)

Calculated value: 57.68 : 5.11 : 14.95
Actual measurement: 57.97 : 5.27 : 14.95
[0157] IR KBrnu cm-1:1712, 1626, 1496, 1452, 1276
[0158] Example of reference 3.2-amino-N-(4-chlorophenyl)-3-(4-methyl piperazino) benzamide [0159] N-(4-chlorophenyl)-2-nitro-3-(4-methyl piperazino) benzamide obtained in the example 2 of reference Ethanol is made to suspend 6.0g and it is stannic-chloride dihydrate. 28g was added and heating reflux was carried out for 30 minutes. The solvent was distilled off under reduced pressure after cooling a reaction mixture. The residue which might be distilled off was poured out into iced water and it extracted with ethyl-acetate ester. The sodium-hydroxide water solution washed the extract 40%, the saturation brine after rinsing washed, and it dried with magnesium sulfate. The crystal which was able to obtain the solvent after distilling off under reduced pressure is ******ed from ethanol, and it is a 2-amino-N-(4-chlorophenyl)-3-(4-methyl piperazino) benzamide. 5.7g (99% of yield) was obtained as a light yellow needle shape crystal. The 202 to 203 degree C melting point.
[0160] Elemental-analysis value C17H19ClN4O It carries out and is [0161].
C(%) H(%) N(%)
Calculated value: 62.69 : 6.14 : 16.25
Actual measurement: 62.48 : 6.35 : 16.10
[0162] IR KBrnu cm-1:3454, 3352, 3286, 2794, 1644, 1596
[0163] 1 H-NMR (CDCl3) delta ppm: -- 7.83 (1H, m), 7.50 (2H, m), 7.27, (2H, m), 7.26-7.07 (2H, m), 6.63 (1H, t) and 5.93 (2H, br s), and 2.95- 2.48 (8H, m) and 2.35 (3H, s)
[0164] Example of reference 4.3-chloro-N-[4-(trifluoromethyl) phenyl]-2-nitro benzanilide [0165] 3-chloro-2-nitro benzoic acid 10g, thionyl chloride The overheating reflux of the mixture of the dimethylformamide of 30ml and the amount of catalysts was carried out for 3 hours. It is a methylene chloride about the acid chloride which distilled off the superfluous thionyl chloride after cooling and was obtained. It was made to dissolve in 15ml and used for the next reaction.
[0166] p-trifluoro methylaniline 6.4g and pyridine It is a methylene chloride about 3.16g. It was made to dissolve in 100ml and the methylene chloride solution of the acid chloride previously obtained under ice-cooling was dropped. It pours into iced water, after agitating reaction mixture at a room temperature for 2 hours, the depositing crystal is ****(ed) and it washes with water and the ether, and it is a 3-chloro-N-[4-(trifluoromethyl) phenyl]-2-nitro benzamide. 9.8g (86% of yield) was obtained as a colorless crystal. The 213 to 216 degree C melting point.
[0167] Elemental-analysis value C14H8F3N 2O3 It carries out and is [0168].

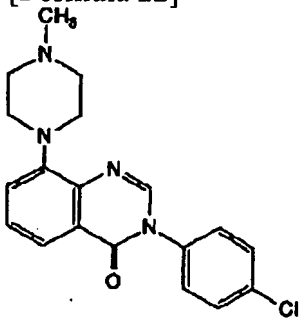
	C (%)	H (%)	N (%)
計算値：	48.78：	2.34：	8.13.
実測値：	48.76：	2.34：	8.16.

[0169] 1 H-NMR (DMSO-d6) delta:7.76 (2H, d), 7.84 (1H, t), 7.89 (2H, d), 7.99 (1H, d), 8.05 (1H, d), 11.18 (1H, br s)
[0170] IR KBrnu cm-1:3360, 1692, 1608, 1538, 1462, 1412, 1370, 1328
[0171] Example of reference 5.3-(4-methyl piperazino)-2-nitro-N-[4-(trifluoromethyl) phenyl] benzamide [0172] 3-chloro-2-nitro-N-[4-(trifluoromethyl) phenyl] benzamide 9.8g, 1-methyl piperazine 4g and anhydrous potassium carbonate 5.52g dimethylformamide In addition to 50ml, it agitated at 100 to 120 degree C for 24 hours. The crystal which poured and deposited in [after cooling a reaction mixture] iced water is ******ed from the ethyl acetate after separation, rinsing, and desiccation, and it is a light-yellow plate crystal about 3-(4-methyl piperazino)-2-nitro-N-[4-(trifluoromethyl) phenyl] benzamide. It obtained as 9.26g (83.4% of yield). The 227 to 230 degree C melting point.
[0173] Elemental-analysis value C19H19F3N 4O3 It carries out and is [0174].
C(%) H(%) N(%)
Calculated value 55.88 : 4.69 : 13.72
Actual measurement 55.70 : 4.63 : 13.62

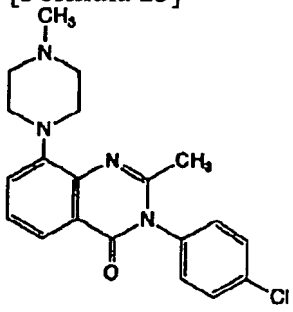
[0175] IR KBrnu cm-1:3256, 2986, 2944, 2800, 1622, 1608
[0176] 1 H-NMR (CDCl3) delta ppm:2.02 (3H, s, NCH3), 2.16-2.33 (4H, m, piperazine 3C, 5 C-H), 2.54-2.78 (4H, m, piperazine 2C, 6 C-H), 7.06-7.55 (6H, m, ArH)
[0177] Example of reference 6.2-amino-3-(4-methyl piperazino)-N-[4-(trifluoromethyl) phenyl] benzamide [0178] 2-amino-3-(4-methyl piperazino)-N-[4-(trifluoromethyl) phenyl] benzamide was obtained like the example 3 of reference. The 188 to 190 degree C melting point.
[0179] 1 H-NMR (CDCl3) delta ppm:7.85 (1H, br s), 7.62 (2H, d), 7.58 (2H, d), 7.21 (2H, m), 6.67 (IH, t), 5.97 (2H, br s)
[0180] Example of reference 7.3-chloro-N-(2-chlorophenyl)-2-nitro benzamide [0181] Like the example 1 of reference, o-chloroaniline 10.5ml is used instead of p-chloroaniline, and it is a 3-chloro-N-(2-chlorophenyl)-2-nitro benzamide. 28.5g (92% of yield) was obtained. The 197 to 198 degree C melting point.
[0182] 1 H-NMR (DMSO-d6) delta ppm:7.31-7.60 (4H, m) and 7.79- 8.10 (3H, m) and 10.6 (1H, br s)
[0183] example of reference 8.N-(4-chlorophenyl)- a 3-[N-[2-(dimethylamino) ethyl]-N-methylamino]-2-nitro benzamide [0184] the example 2 of reference -- the same -- carrying out -- N[from a 3-chloro-N-(4-chlorophenyl)-2-nitro benzamide and N-[2-(dimethylamino) ethyl]-N-monomethylamine]-(4-chlorophenyl)- the 3-[N-[2-(dimethylamino) ethyl]-N-methyl] amino-2-nitro benzamide was obtained. 33% of yield. The 150 to 152 degree C melting point.
[0185] 1 H-NMR (CDCl3) delta ppm:2.21 (6H, s), 2.43 (2H, br t), 2.80 (3H, s) and 3.18 (2H, br t), and 7.15- 7.54 (7H, m) and 7.86 (1H, br s)
[0186] example of reference 9.2-amino-N-(4-chlorophenyl)- 3-[N-[2-(dimethylamino) ethyl]-N-methylamino] benzamide [0187] The 2-amino-N-(4-chlorophenyl)-3-[N-[2-(dimethylamino) ethyl]-N-methylamino] benzamide was obtained like the example 3 of reference. Melting point 94 to 95 degree C.

[0188] 1 H-NMR (CDCl3) delta ppm:7.76 (1H, s), 7.52 (2H, d), 7.31 (2H, d), 7.22 (1H, dd), 7.14 (1H, dd), 6.63 (1H, dd), 6.45 (2H, br s), 2.92 (2H, t), 2.69 (3H, s), 2.44 (2H, t), 2.28 (6H, s)
[0189] Example of reference 10.3-chloro-(4-chlorophenyl)-N-ethoxy carbonylmethyl-2-nitro benzamide
[0190] The approach of the example 1 of reference is followed and it is N-(4-chlorophenyl) glycine instead of p-chloroaniline. Ethyl ester 11.34g is used and it is a 3-chloro-N-(4-chlorophenyl)-N-ethoxy carbonylmethyl-2-nitro benzamide. 17.3g (90.3% of yield) was obtained as prism **. The 119 to 121 degree C melting point.
[0191] 1 H-NMR (CDCl3) delta ppm:1.31 (3H, t), 4.26 (2H, q) and 4.52 (2H, s), 7.00-7.48 (7H, m)
[0192] example of reference 11.N-(4-chlorophenyl)-3 -- a - [N-[2-(dimethylamino) ethyl]-N-methylamino]-N-ethoxy carbonylmethyl-2-nitro benzamide [0193] 3-chloro-N-(4-chlorophenyl)-N-ethoxy carbonylmethyl-2-nitro benzamide obtained in the example 10 of reference 5g and N and N, N'-trimethyl ethylenediamine 5.7ml is stirred at 100 to 105 degree C under a nitrogen air current for 2.5 hours. It flows into water after cooling and chloroform extracts. It condensed after drying a chloroform layer. the column chromatography [residue] using silica gel -- refining -- N-(4-chlorophenyl)-3 - [N-[2-(dimethylamino) ethyl]-N-methylamino]-N-ethoxy carbonylmethyl-2-nitro benzamide 5.8g (99% of yield) was obtained as a pale-red-color candy-state object.
[0194] 1 H-NMR (CDCl3) delta ppm:1.30 (3H, t), 2.20 (6H, s), 2.41 (2H, t), 2.79 (3H, s), 3.17 (2H, t), 4.24 (2H, q) and 4.51 (2H, s), 6.57-7.40 (7H, m)
[0195] Example of reference 12.2-amino-N-(4-chlorophenyl)-3-[N-[2-(dimethylamino) ethyl [-N-methylamino]-N-ethoxy carbonylmethyl-benzamide [0196] N-(4-chlorophenyl)-3-[N-[2-(dimethylamino) ethyl]-N-methylamino]-N-ethoxy carbonylmethyl-2-nitro benzamide obtained by example of reference 11 7.5g and stannic-chloride dihydrate It is ethanol about 12.8g. Heating reflux is carried out among 200ml for 2 hours. A solvent is distilled off after cooling and it is ethyl acetate about residue. Subsequently saturation brine washes 150ml of 40% sodium-hydroxide water solutions which diluted with 100ml and were cooled on ice. An ethyl acetate layer is dried with a sodium sulfate. a solvent -- distilling off -- 2-amino-N-(4-chlorophenyl)- 3-[N-[2-(dimethylamino) ethyl]-N-methylamino]-N-ethoxy carbonylmethyl-benzamide 5.3g (76% of yield) was obtained as a light yellow

candy-state object.
[0197] 1 H-NMR (CDCl3) delta ppm:1.31 (3H, t), 2.32 (6H, s), 2.45 (2H, t), 2.58 (3H, s), 2.90 (2H, t), 4.25 (2H, q) and 4.53 (2H, s), 6.36-7.45 (7H, m)
[0198]
[Example]
Example 1.3-(4-chlorophenyl)-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0199]
[Formula 22]

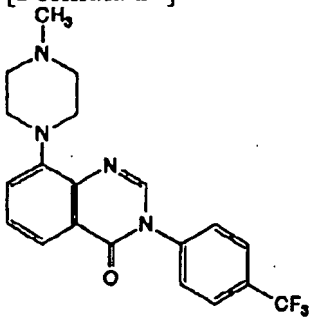


[0200] 2-amino-N-(4-chlorophenyl)-3-(4-methyl piperazino) benzamide obtained in the example 3 of reference 4.0g and triethyl orthoformate The concentrated sulfuric acid of the amount of catalysts was added to 30ml mixture, and it agitated at 110 degrees C for 1.5 hours. Saturation sodium bicarbonate underwater was filled with the reaction mixture after cooling, and ethyl acetate extracted. It is 3-(4-chlorophenyl)-8-(4-methyl piperazino)-3 and 4-dihydroquinazoline by saturation brine's washing an organic layer, distilling off a solvent after desiccation with magnesium sulfate, and recrystallizing [ethanol]. - 4 - It turns on. 3.8g (92% of yield) was obtained. The 140 to 142 degree C melting point.
[0201] Elemental-analysis value C19H19ClN4O It carries out and is [0202].
C(%) H(%) N(%)
Calculated value: 64.31 : 5.40 : 15.79
Measured value: 64.55 : 5.56 : 15.99
[0203] 1 H-NMR (CDCl3) 7.98 (1H, dd) delta:2.40 (3H, s), 2.76 (4H, m) and 3.38 (4H, m), 7.27-7.58 (6H, m), 8.08 (1H, s)
[0204] Example 2.3-(4-chlorophenyl)-2-methyl-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0205]
[Formula 23]

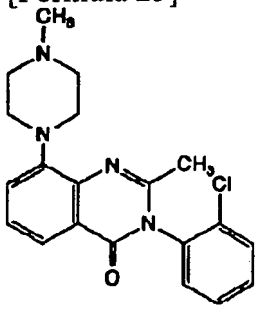


[0206] the 2-amino-N-(4-chlorophenyl)-3-(4-methyl piperazino) benzamide and alt.acetic-acid triethyl which were obtained in the example 3 of reference as well as the case of an example 1 from -- 3-(4-chlorophenyl)-2-methyl-8-(4-methyl piperazino)-3 and 4-dihydroquinazoline-4-ON It obtained. The 221 to 223 degree C melting point.
[0207] Elemental-analysis value C20H21ClN4O It carries out and is [0208].
C(%) H(%) N(%)
Calculated value: 65.12 : 5.74 : 15.19
Measured value: 65.05 : 5.63 : 15.11
[0209] 1 H-NMR (CDCl3) 7.52 (2H, d) delta:2.26 (3H, s), 2.40 (3H, s), 2.75 (4H, m), 3.40 (4H, m) and

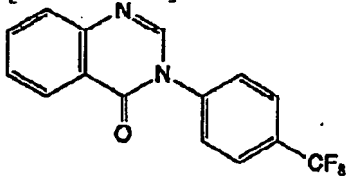
7.15 (2H, d), 7.26-7.38 (2H, m), 7.89 (1H, dd)
[0210] Example 3.8-(4-methyl piperazino)-3-[4-(trifluoromethyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0211]
[Formula 24]



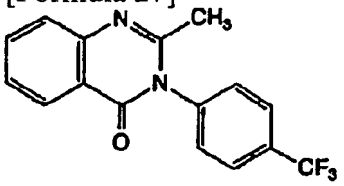
[0212] 8-(4-methyl piperazino)-3-[4-(trifluoromethyl) phenyl]-3 and 4-dihydroquinazoline-4-ON was obtained from 2-amino-3-(4-methyl piperazino)-N-[4-(trifluoromethyl) phenyl] benzamide and the triethyl orthoformate which were obtained in the example 6 of reference like the case of an example 1. The 151 to 153 degree C melting point.
[0213] Elemental-analysis value C20H19F3N4O It carries out and is [0214].
C(%) H(%) N(%)
Calculated value: 61.85 : 4.93 : 14.43
Measured value: 61.83 : 4.98 : 14.59
[0215] 1 H-NMR (CDCl3) delta:2.41 (3H, s), 2.75 (4H, m) and 3.35 (4H, m), 7.26-7.70 (2H, m), 7.56 (2H, d), 7.83 (2H, d), 7.95 (1H, dd), 8.12 (1H, s)
[0216] Example 4.3-(2-chlorophenyl)-2-methyl-8-(4-methyl piperazino)-3, 4-dihydroquinazoline-4-ON [0217]
[Formula 25]



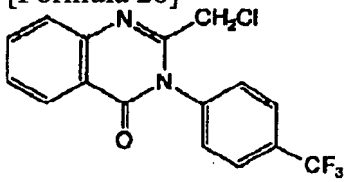
[0218] 3-(2-chlorophenyl)-2-methyl-8-(4-methyl-1-piperazinyl)-3 and 4-dihydroquinazoline-4-ON was obtained from the 2-amino-N-(2-chlorophenyl)-3-(4-methyl piperazino) benzamide and alt.acetic-acid triethyl which were obtained in the example 3 of reference like the case of an example 1. The 111 to 113 degree C melting point.
[0219] 1 H-NMR (CDCl3) delta:2.39 (3H, m), 2.60 (4H, m), 2.96 (5H, m) and 6.70 (1H, t), 6.95-7.46 (5H, m), 8.30-8.52 (2H, m)
[0220] Example 5.3-[4-(trifluoromethyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0221]
[Formula 26]



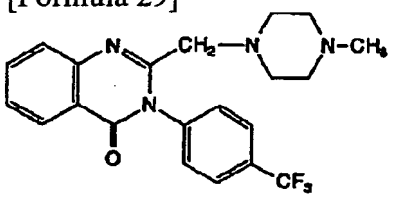
[0222] 3-[4-(trifluoromethyl) phenyl]-3 and 4-dihydroquinazoline-4-ON was obtained from 2-amino-N-[4-(trifluoromethyl) phenyl] benzamide and the triethyl orthoformate like the case of an example 1. The 211 to 213 degree C melting point.
[0223] Elemental-analysis value C15H19F3N2O It carries out and is [0224].
C(%) H(%) N(%)
Calculated value: 62.07 : 3.13 : 9.65
Measured value: 61.91 : 2.90 : 9.59
[0225] 1 H-NMR (CDCl3) 8.11 (1H, s) delta:7.46-7.89 (8H, m), 8.36 (1H, m)
[0226] Example 6.2-methyl-3-[4-(trifluoromethyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0227]
[Formula 27]



[0228] 2-methyl-3-[4-(trifluoromethyl) phenyl]-3 and 4-dihydroquinazoline-4-ON was obtained from 2-amino-N-[4-(trifluoromethyl) phenyl] benzamide and alt.acetic-acid triethyl like the case of an example 1. The 156 to 158 degree C melting point.
[0229] Elemental-analysis value C16H21F3N2O It carries out and is [0230].
C(%) H(%) N(%)
Calculated value: 63.16 : 3.64 : 9.21
Measured value: 63.05 : 3.31 : 9.16
[0231] 1 H-NMR (CDCl3) delta:2.23 (3H, s) and 7.38- 7.88 (7H, m) and 8.23 (1H, d)
[0232] Example 7.2-chloromethyl-3-[4-(trifluoromethyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0233]
[Formula 28]

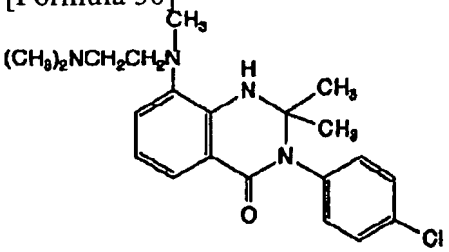


[0234] 2-amino-N-[4-(trifluoromethyl) phenyl] benzamide 4.2g acetic acid In 30ml solution Chloroacetyl chloride 3.6ml was dropped and it agitated at 110 degrees C for 4 hours. The solvent was distilled off after cooling, water was added to residue, potassium carbonate neutralized, and ethyl acetate extracted. The organic layer was dried with potassium carbonate after washing with saturation brine. A solvent is distilled off, and it recrystallizes [ethanol] after purification with a column chromatography, and is 2-chloromethyl-3-[4-(trifluoromethyl) phenyl]-3 and 4-dihydroquinazoline. - 4 - It turns on. 3.2g (64% of yield) was obtained. The 124 to 126 degree C melting point.
[0235] 1 H-NMR (CDCl3) delta:4.26 (2H, s) and 7.47- 7.90 (7H, m) and 8.29 (1H, m)
[0236] Example 8.2-(4-methyl piperazino) methyl-3-[4-(trifluoromethyl) phenyl]-3, 4-dihydroquinazoline-4-ON [0237]
[Formula 29]

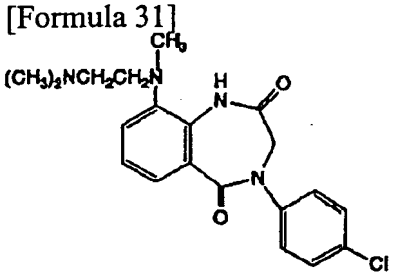


[0238] 2-chloromethyl-3-[4-(trifluoromethyl) phenyl]-3 and 4-dihydroquinazoline-4-ON 2.4g dimethylformamide obtained in the example 7 It is 1-methyl piperazine to 10ml. 1.2ml and anhydrous

potassium carbonate 1.16g was added and it agitated at the room temperature for 1.5 hours. The reaction mixture was poured out into iced water, the depositing crystal was separated, it recrystallized [ethanol], and 2-(4-methyl piperazino) methyl-3-[4-(trifluoromethyl) phenyl]-3 and 4-dihydroquinazoline-4-ON (79% of yield) was obtained. The 197 to 199 degree C melting point.
[0239] Elemental-analysis value C21H21F3N4O It carries out and is [0240].
C(%) H(%) N(%)
Calculated value: 62.68 : 5.26 : 13.92
Measured value: 62.98 : 5.29 : 13.56
[0241] 1 H-NMR (CDCl3) delta:1.75 (2H, m), 2.25 (7H, m) and 2.77 (4H, m), and 7.26- 7.79 (7H, m) and 8.25 (1H, m)
[0242] Example 9.3-(4-chlorophenyl)-2, 2-dimethyl-8-[N-(2-dimethylaminoethyl) amino-N-methyl]-1, 2 and 3, 4-tetrahydro quinazoline-4-ON [0243]
[Formula 30]



[0244] N-(4-chlorophenyl)-2-amino-3-[N-(2-dimethylaminoethyl) amino-N-methyl] benzamide obtained in the example 9 of reference 5.00g, Para toluenesulfonic acid 3.00g and acetone The heating reflux of the 200ml mixture was carried out for 40 minutes. It is 10% potassium carbonate water solution after cooling and to a reaction mixture. 20ml was added and the solvent was distilled off. Chloroform was added to residue and it dried with the sodium sulfate (anhydrous) after rinsing. The residue which distilled off the solvent was given to the silica gel column chromatography (methanol: chloroform 1:9), and was refined. Furthermore, it recrystallizes from the chloroform-ether and is the colorless crystal of 3-(4-chlorophenyl)-2, 2-dimethyl-8-[N-(2-dimethylaminoethyl) amino-N-methyl]-1, 2 and 3, and 4-tetrahydro quinazoline-4-ON. 4.81g (86% of yield) was obtained. The 151 to 152 degree C melting point.
[0245] Elemental-analysis value C21H27ClN4O It carries out and is [0246].
C(%) H(%) N(%)
Calculated value: 65.19 : 7.03 : 14.48
Actual measurement: 65.04 : 7.00 : 14.29
[0247] 1 H-NMR (CDCl3) delta:1.45 (6H, s), 2.32 (6H, s), 2.44 (2H, br t), 2.70 (3H, s), 2.86 (2H, br t) and 6.72 (2H, d), and 7.0- 7.3 (3H, m), 7.36 (2H, d), and 7.64(1H, d). [0248] Example 10.4-(4-chlorophenyl)-9-[N-(2-dimethylaminoethyl)-N-methylamino]-2, 3 and 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione [0249]
[Formula 31]



[0250] 2-amino-N-(4-chlorophenyl)-3-[N-(2-dimethylaminoethyl)-N-methylamino]-N-ethoxy carbonylmethyl benzamide obtained in the example 12 of reference 4g and triethylamine It is toluene about 3.9ml. Heating reflux is carried out for three days in 200ml and under a nitrogen air current. After

cooling, a solvent is distilled off and residue is dissolved in chloroform. After 0.2-N sodium-hydroxide water solution and saturation brine wash a chloroform layer one by one, it dries using a sodium sulfate. The crystal obtained by distilling off a solvent is ******ed from isopropanol-isopropyl ether, and it is 4-(4-chlorophenyl)-9-[N-(2-dimethylaminoethyl)-N-methylamino. - 2, 3, 4, 5-tetrahydro-1H-1, the 4-benzodiazepine -2, 5-dione 2.5g (70% of yield) was obtained as prism **. The 139 to 141 degree C melting point.

[0251] Elemental-analysis value C20H23ClN 4O2 It carries out and is [0252].

C(%) H(%) N(%)

Calculated value: 62.09 : 5.99 : 14.48

Actual measurement: 62.12 : 5.96 : 14.75

[0253] 1 H-NMR (CDCl3) delta:2.39 (8H, br), 2.76 (3H, s), 2.91 (2H, br) and 4.22 (2H, s), 7.21-7.77 (7H, m)

[0254] Mass spectrum (FAB): 387M+ [0255]

[Test Example(s)]

Example of trial 1. rat adjuvant arthritis (AA) evaluation system trial [0256] The trial was presented by making a 8-weeks old feminity Lewis (Lewis) system rat (Charles River Japan) into seven-animal one group. 0.6mg (Difco) of the Mycobacterium BUCHIRIKAMU (Mycobacterium butyricum) heating killed bacteria suspended in the liquid paraffin as an adjuvant and 0.1ml were inoculated into the left hind-foot planta of the Lewis system rat, and arthritis was induced. The examined substance was suspended [ml] in 10mg /in the solvent which consists of 0.5% carboxymethyl cellulose of Tween 80 addition 0.03%, and it administered orally by the dosage of 50mg/ml/kg for 1 time per, 6 times per week, and three weeks day 20 days after adjuvant inoculation that day. The symptoms control group was similarly medicated with the solvent. 27 days after adjuvant inoculation, six steps of mark (0-5 points) were given, extent of the inflammation in six places of a right hind foot, a right-and-left forelimb, a right-and-left lug, and a tail was evaluated, respectively, and the number of marks total was made into arthritis mark. Each group calculated average arthritis mark from the average of seven animals, and it asked for the rate of arthritis mark control of an examined substance from the bottom type. A result is shown in Table 1.

[0257] Average arthritis mark of rate (%) of arthritis mark control =100x (average arthritis mark of the average arthritis mark-examined substance group of a symptoms control group) / symptoms control group

[0258] This evaluation system is a model of polyarthritis whose symptoms the immune response to Mycobacterium BUCHIRIKAMU is attracted, and are shown, and what shows depressant action by this evaluation system is useful as the preventive of an inflammatory disease especially the inflammation accompanying rheumatism, or a bone disease or a therapy agent, and an antirheumatic drug.

[0259] The plaque forming cell (PFC) trial which detects the SRBC antigen specific IgM antibody production splenic cells by example of trial 2. sheep erythrocyte (SRBC) immunity [0260] The trial was presented by making a 8-weeks old feminity BDF1 mouse (Charles River Japan) into seven-animal one group. SRBC Immunity of 4x108 pieces / the 0.2ml was inoculated and carried out to BDF1 mouse intraperitoneal. The examined substance was suspended [ml] in 5mg /in the solvent which consists of 0.5% carboxymethyl cellulose of Tween 80 addition 0.03%, and it administered orally by the dosage of 50mg / 10ml/kg once per day three days after immunity that day. The negative control group was similarly medicated with the solvent. The spleen was taken out four days after immunity and splenic-cells suspension was filled to Cunningham's chamber with SRBC and complement according to Cunningham's (Cunningham) direct method (Cunningham A.J.& Szenberg A., Further improvements in the plaque technique for detecting single antibody-forming cells., Immunology, 14,599-600, 1968.). The PFC number was measured after 1-hour standing at 37 degrees C, and it converted into the PFC number per spleen. Each group calculated the PFC number per average spleen from the average of seven animals, and it asked for the rate of PFC control of an examined substance from the bottom type. t trial of Student performed statistics processing, and when significant ($p < 0.05$), * was given to the result. A result is shown in Table 1.

[0261] It is a PFC number per average spleen of rate (%) of PFC control =100x (per average spleen of a negative control group per average spleen of a PFC number-examined substance group PFC number) / negative control group.

[0262] An exam system is a model of humoral immunity with which a B cell produces an anti-S RBC antibody to a T cell dependency, and what shows depressor effect by this evaluation system is useful as the preventive of immune diseases, such as rheumatism or allergy, or a therapy agent, and an immunosuppressive agent.

[0263]

[Table 1]

化合物 実施例番号	試験例1 (%)	試験例2 (%)
2	41	34*
3	33	-
9	46	55*
10	29	-

[0264]

[Effect of the Invention] The bicyclic compound of this invention showed significant depressor effect by the immune response trial system of a mouse, i.e., the plaque forming cell (PFC) trial system which detects the SRBC antigen specific IgM antibody production splenic cells by sheep erythrocyte (SRBC) immunity. Furthermore, the rat adjuvant arthritis (AA) which is the symptoms model of rheumatoid arthritis showed the symptoms improvement effect. Therefore, the bicyclic compound of this invention is useful as an antirheumatic drug.

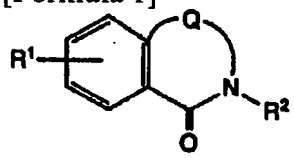
[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

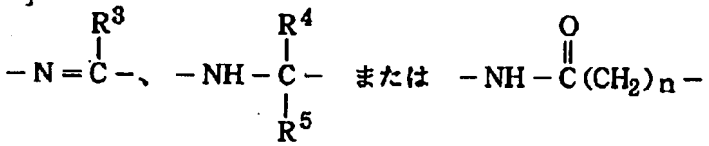
CLAIMS

[Claim(s)]
[Claim 1] General formula (I)
[Formula 1]



(I)

R1 means among [type the nitrogen-containing heterocycle radical which has the amino group, nitrogen-containing heterocycle radical, or substituent which has a hydrogen atom, an amino group, and a substituent. R2 means the aryl group which has an aryl group or a substituent. Q is a general formula [** 2].



(R3 means among a formula the alkyl group which has a hydrogen atom, an alkyl group, or a substituent.) R4 means a hydrogen atom or an alkyl group. R5 means a hydrogen atom or an alkyl group. n means 1 or 2. It expresses.] The bicyclic compound come out of and shown, and its salt [claim 2] Physic [claim 3] which makes an active principle a bicyclic compound or its salt according to claim 1 The preventive or the therapy agent [claim 4] of the immune disease which makes an active principle a bicyclic compound or its salt according to claim 1, and/or an inflammatory disease The preventive with unusual immunity or the therapy agent [claim 5] accompanying the rheumatism or allergy which makes an active principle a bicyclic compound or its salt according to claim 1 The preventive or the therapy agent [claim 6] of an inflammatory disease accompanying the rheumatism or allergy which makes an active principle a bicyclic compound or its salt according to claim 1 The preventive or the therapy agent [claim 7] of a bone disease which makes an active principle a bicyclic compound or its salt according to claim 1 The antirheumatic drug which makes an active principle a bicyclic compound or its salt according to claim 1 [claim 8] The immunosuppressive agent which makes an active principle a bicyclic compound or its salt according to claim 1

[Translation done.]